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Experimental Therapeutics

MS-27-275, an Inhibitor of Histone Deacetylase, Has Marked *in Vitro* and *in Vivo* Antitumor Activity against Pediatric Solid Tumors

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The antitumor efficacy of the synthetic benzamide derivative MS-27-275 (MS-275), an inhibitor of histone deacetylation [T. Suzuki *et al.*, *J. Med. Chem.*, 42: 3001-3003, 1999], was evaluated in a series of pediatric solid tumor cell lines, including neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma (EWS), retinoblastoma, medulloblastoma, undifferentiated sarcoma (US), osteosarcoma, and malignant rhabdoid tumors. Treatment with MS-275 results in an increase in acetylation of histones within 4 h of drug exposure. The cell lines were treated with various concentrations of MS-275 for 3 days and incubated with [³H]thymidine for 20 h before cell harvest. MS-275 inhibited [³H]thymidine uptake in a dose-dependent manner in all tumor cell lines examined. The IC₅₀ ranged from 50 nm in the D283 medulloblastoma cell line to 1.3 μ M in the US. A common feature of MS-275 treatment of pediatric tumor cell lines was induction of p21 mRNA. However, the effects on cell cycle were diverse because in some cases MS-275 induced an increase in G₁ or G₂, whereas in others, there was an induction of apoptosis. In EWS, the EWS/fli chimeric transcription factor created by the t(11;22) suppresses transforming growth factor (TGF) β RII transcription, however, MS-275 was able to induce an increase in TGF- β RII mRNA and restore TGF- β signaling. Using xenograft orthotopic models of US, EWS, and neuroblastoma, we find that the growth of established tumors is inhibited in mice treated with MS-275.